Clinical Investigation

Cimetidine Therapy for Gastroesophageal Reflux Disease

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In a Canadian multicenter trial, a new dosing regimen of cimetidine (Tagamet)—600 mg given twice a day—was compared with the standard regimen of 300 mg four times a day in 118 evaluable patients with endoscopically proved esophagitis. More than 90% of the patients evaluated had clinically moderate to severe esophagitis. After four weeks of therapy, both regimens had significantly reduced the number of episodes and the severity and duration of the worst episodes of daytime and nighttime heartburn, as evaluated by visual analogue scales. After eight weeks of therapy, this improvement persisted. There was no difference between the regimens. Healing was observed endoscopically in 57% of patients receiving cimetidine 300 mg four times a day and in 55% of those receiving 600 mg twice a day. Side effects were infrequent and minor.

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The symptomatic treatment of gastroesophageal reflux disease consists of dietary and posture manipulations, weight reduction and avoiding excess alcohol, caffeine-containing beverages and tobacco products. Therapeutic agents include antacids, metoclopramide hydrochloride and H_2-receptor antagonists. Cimetidine is widely used in the treatment of this disease. In treating patients in North America who have acid-pepsin disease, cimetidine (Tagamet) is usually used in a dosage regimen of 300 mg taken four times a day with meals and at bedtime. In treating patients with duodenal ulcer disease, however, it has recently been shown that cimetidine, 600 mg given twice a day, is more effective than 300 mg taken four times a day in relieving nighttime pain and of equal efficacy in the healing of ulcers (P. Pare, A. Archambault and A. B. R. Thomson, unpublished observations, 1985). Accordingly, the present study was undertaken to compare the therapeutic efficacy of cimetidine, 600 mg given twice a day, with that of cimetidine, 300 mg four times a day, in cases of gastroesophageal reflux disease.

This was a multicenter Canadian trial in which eligible patients were randomly selected to receive an eight-week course of open-label cimetidine (Tagamet, Smith Kline & French Canada Ltd), 300 mg four times a day or 600 mg twice a day. Symptomatic improvement was assessed by interview after four and eight weeks of therapy. A repeat endoscopy was done at the eight-week visit.

Patients and Methods

Patient Selection

Patients 18 years and older with endoscopic evidence of esophagitis were considered eligible for the study. Their primary complaint was usually heartburn, defined as a retrosternal burning discomfort occurring during the day, at night or both. Patients were excluded if they had a concomitant gastric or duodenal ulcer or scleroderma. Pregnant and lactating women or those not on a medically acceptable contraceptive regimen were not considered eligible for entry into the study. Patients were also excluded if they had had a gastric operation or vagotomy, a history of significant alcohol abuse or were required to remain on long-term drug therapy, including antineoplastic agents, anticoagulants, metoclopramide, anticholinergics, phenothiazines or thioureas. The occasional use of salicylates, phenylbutazone, indomethacin, benzodiazepines and antacids was permitted and a record of their use was kept. Treatment with H_2-receptor antagonists

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for more than one week before the screening endoscopy excluded potential subjects.

The protocol was approved by the ethics review committee in each participating center. All patients provided written informed consent.

Upon entering, patients were advised to moderate their intake of alcohol, caffeine-containing beverages and tobacco. They were also advised to elevate the heads of their beds 15 cm (6 in) and to avoid stooping and bending after meals. Compliance was checked at each visit by a pill count.

Assessment of Symptomatic Improvement

Symptomatic assessments were conducted at pretreatment and after four and eight weeks of therapy. The average number of episodes and the severity and duration of the worst episode of daytime and nighttime heartburn were assessed using 100-mm visual analogue scales that were completed by the patient. The patient was presented with each question twice in random order. The mean of the two responses was recorded for analysis. The presence and severity of dysphagia, flatulence, nausea and vomiting were assessed by interview, as was the frequency of heartburn after meals and while the patient was bending or lying down.

Endoscopic Assessment of Improvement

Endoscopy was done before treatment and after eight weeks of therapy, usually by the same physician. The appearance of the esophageal mucosa was graded as follows:

Grade 1—normal
Grade 2—hyperemia or opaque mucosa
Grade 3—friability or granular exudate without a discrete lesion
Grade 4—erosions and discrete lesions that cannot be wiped or washed away
Grade 5—ulceration

Grade 2 esophagitis was confirmed by a positive result on a Bernstein test. The appearance of the stomach and duodenal mucosa was also noted. Healing of the esophagitis was defined as grades 3, 4 and 5 resolving to grade 2 or 1, and grade 2 resolving to grade 1. Endoscopic improvement was considered to have occurred if the severity of the esophagitis had declined by at least one grade after eight weeks of therapy.

Statistical Analysis

From the line assessment data of frequency, severity and duration of heartburn, the treatment effect for both regimens was evaluated using the Wilcoxon matched pairs signed-ranks test. The Mann-Whitney U test was used to evaluate any difference between the two regimens. All frequency data were subjected to a χ^2 test, and the Student's t test was used to evaluate differences between the two groups with respect to age, length of illness and duration of relapse. The level of significance was set at $P < .05$.

Results

Patient Population

In total, 153 patients were enrolled in the study. However, 18 patients did not meet acceptable entry criteria and 17 did not complete the eight weeks of therapy: 7 refused to continue through the full eight weeks, 5 had an intercurrent illness, 3 were withdrawn after experiencing an adverse reaction and 3 were removed after two and four days of treatment due to insufficient therapeutic effect. To evaluate the effect of excluding these 35 patients from analysis, the healing rates were recalculated with these patients included as failures. There was no significant change in the interpretation of the results.

TABLE 1.—*Demographic Data of 118 Patients in a Multicenter Canadian Study of Cimetidine Therapy*

Patient Characteristics	Treatment Regimen: Cimetidine 300 mg qid* N = 60	Treatment Regimen: Cimetidine 600 mg bid* N = 58
Age, yr	45.7 ± 14.5	46.0 ± 13.4
Sex ratio, male:female	39:21	44:14
Duration of disease, yr	6.2 ± 6.4	9.4 ± 9.1
Duration of current episode, yr	3.0 ± 5.0	4.1 ± 7.3
Patients who previously used H_2-receptor antagonists, No.	26	24

bid = twice a day, qid = four times a day

*Mean ± standard deviation.

Of the 118 evaluable patients, 60 received cimetidine, 300 mg four times a day, and 58 received cimetidine, 600 mg twice a day. The patient demographics at study entry were similar in both groups (Table 1). There were 83 men and 35 women, aged an average of 45.6 years. About 40% of these patients had received H_2-antagonist therapy for varying periods in the past. Most of the patients had previously used antacids for pain relief and had been given advice about avoiding bending and lifting after meals and elevating the heads of their beds.

Antacid consumption was monitored at each visit and found to be minimal in both groups. Thirteen patients in each regimen occasionally used small amounts of antacids of their choice.

Symptomatic Evaluation

After four weeks of either regimen, there was a significant ($P < .001$) reduction in the number of episodes of heartburn and the severity and duration of the worst episodes of daytime heartburn, as measured by the visual analogue scales (Figure 1). The scores at eight weeks were also significantly lower when compared with pretreatment scores. When the eight-week scores were compared with those obtained after four weeks of therapy, only the 300-mg four-times-a-day regimen provided further significant improvement for the number of episodes ($P < .05$); only cimetidine, 600 mg taken twice a day, produced further significant reduction in the duration of the worst episode ($P < .05$). Both regimens significantly reduced the severity of the worst episode of daytime heartburn. A significant difference between regimens favoring cimetidine, 300 mg taken four times a day, was detected for the severity of the worst episode at eight weeks. There was no statistical difference between the two regimens for any other assessment.

There was also a significant reduction ($P < .001$) in the number of episodes and in the duration and severity of the worst episode of nighttime heartburn after four weeks and eight weeks of therapy when compared with pretreatment (Figure 2). Further significant improvement occurred between four and eight weeks of therapy only for the severity of the worst episode of heartburn and only with the 300-mg

four-times-a-day regimen of cimetidine. At no time was there any difference between regimens in relieving the symptoms of nighttime heartburn.

In all, 24 patients in the 300-mg four-times-a-day group and 20 patients receiving cimetidine, 600 mg twice a day, reported dysphagia on entry into the study. These numbers were reduced to 15 and 6, respectively, after four weeks of therapy, and to 13 and 9, respectively, after eight weeks of cimetidine. The pretreatment incidence of flatulence, nausea and vomiting was low. Improvement occurred over the course of therapy and no difference was found in favor of either regimen.

At pretreatment, 90% of patients receiving 300 mg four times a day of cimetidine and 97% of patients receiving 600 mg twice a day complained of heartburn after meals. Of these, 31 on each regimen reported experiencing these symptoms frequently. After four weeks of therapy, only four patients receiving cimetidine, 300 mg four times a day, and eight patients receiving 600 mg twice a day continued to complain of frequent heartburn. Before entering the study, more than 70% of patients on both regimens of cimetidine complained of heartburn symptoms after bending or lying down. Fewer than ten patients on either regimen complained of frequent symptoms after four weeks of therapy with cimetidine. Symptomatic improvement was maintained at eight weeks. At no time was a difference detected in favor of either regimen in relieving the frequency of heartburn symptoms after meals or while bending or lying down.

Endoscopic Evaluation

At pretreatment, more than 90% of the patients had endoscopic findings of grade 3 esophagitis or worse. The distribution of the endoscopic grading was similar in the two treatment groups (Figure 3). After eight weeks of therapy with cimetidine, there was a dramatic reduction in the proportion of patients with grades 5, 4 and 3 esophagitis. Healing was observed in 57% of patients treated with cimetidine, 300 mg four times a day, and in 55% of patients receiving 600 mg twice a day of cimetidine. No difference was noted between the two treatment groups with respect to the distribution of the endoscopic grades after eight weeks of therapy.

As shown in Figure 3, improvement occurred in all grades of esophagitis. For example, 19 (73%) patients with grade 4 esophagitis receiving cimetidine, 300 mg four times a day, and 21 (88%) patients with grade 4 esophagitis receiving 600 mg twice a day showed improvement endoscopically with treatment. Of these, 17 (65%) receiving 300 mg four times a day and 19 (79%) receiving 600 mg twice a day were considered healed. Worsening of the endoscopic grade occurred only in the group of 26 patients presenting with grade 3 esophagitis. Three receiving 300 mg four times a day and one receiving 600 mg twice a day had worsening of the endoscopic grade. The demographic data for these patients did not differ significantly from the rest of the patient population.

A total of 36 patients had associated gastritis, duodenitis or both; 35 (97%) of these had grade 3 esophagitis or worse. After eight weeks of therapy, the gastritis or duodenitis had healed in 29 patients (81%). These lesions failed to heal in

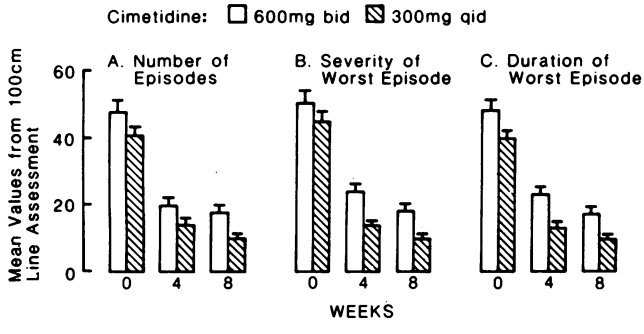

Figure 1.—Symptomatic evaluation of daytime heartburn. bid = twice a day, qid = four times a day

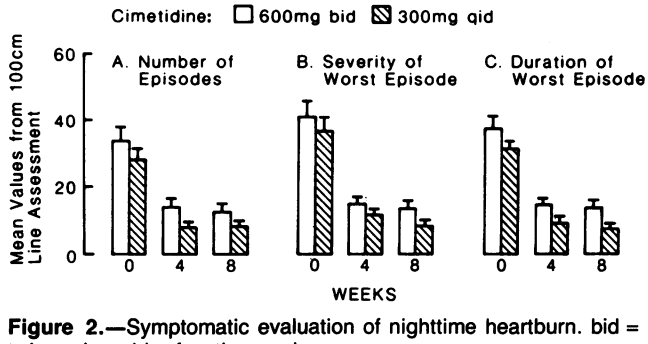

Figure 2.—Symptomatic evaluation of nighttime heartburn. bid = twice a day, qid = four times a day

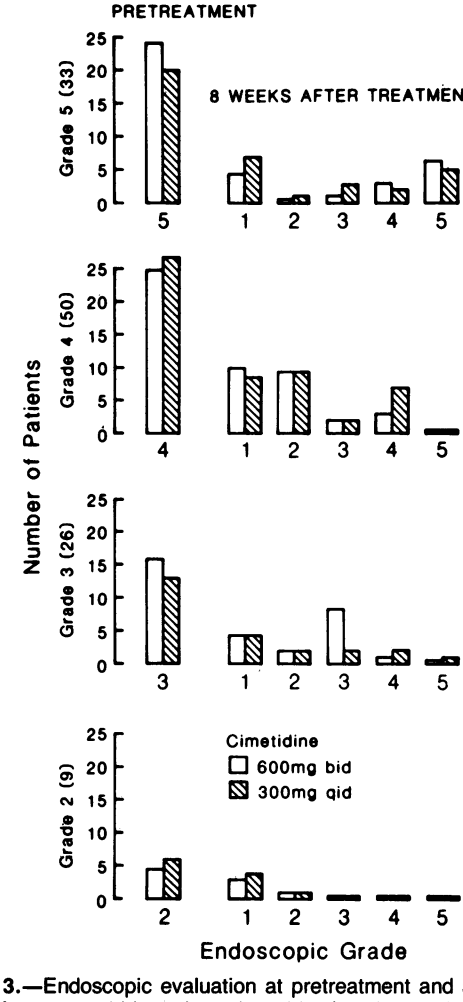

Figure 3.—Endoscopic evaluation at pretreatment and after eight weeks of treatment. bid = twice a day, qid = four times a day

seven patients: in three patients receiving cimetidine, 300 mg four times a day, and in four patients treated with 600 mg twice a day. In four of the seven patients in whom neither the gastritis nor the duodenitis resolved, the esophagitis also did not heal.

Adverse Reactions Reported

Adverse reactions reported by investigators as being possibly related to therapy are shown in Table 2. Four patients taking cimetidine, 300 mg four times a day, and six patients treated with cimetidine, 600 mg twice a day, complained of adverse reactions. In one person gynecomastia developed after six weeks of treatment. In general, the incidence of adverse reactions was low, and no unusual or unexpected adverse reactions were reported with the use of 600 mg twice a day of cimetidine.

TABLE 2.—*Adverse Reactions Reported*

Cimetidine Dosage	Reaction to Therapy	No. Subjects Reporting	Comments
300 mg qid	Headache	1	Resolved on therapy regimen
	Dizziness, forgetfulness, nausea, weakness	1	Discontinued study
	Loss of libido	1	Resolved poststudy
	Impotence	1	Resolved poststudy
600 mg bid	Rash	2	1-Discontinued study 1-Resolved poststudy
	Diarrhea	1	Resolved on therapy regimen
	Dizziness, general weakness	1	Discontinued study
	Gynecomastia	1	Discontinued study
	Slow pulse	1	Outcome unknown

qid = four times a day, bid = twice a day

Discussion

The pathogenesis of gastroesophageal reflux disease is complex and multifactorial.[1-7] Attention has focused for many years on the incompetence of the lower esophageal sphincter high-pressure zone. Recently, however, interest has been directed to the acid-clearance mechanism, the resistance of the esophageal mucosa, the volume and concentration of acidic gastric juice, duodenal-gastric reflux and the rate of gastric emptying. Furthermore, studies in patients with gastroesophageal reflux disease are difficult both to conduct and to interpret because of the multiple pathogenic mechanisms and the numerous clinical approaches to defining the disorder.[8] The condition may be defined on the basis of symptoms, abnormalities in gross appearance of the esophagus at endoscopy, abnormalities in the esophageal mucosal biopsy specimen, a positive Bernstein test or an abnormal motility pattern.[9] As a result of this complex interplay,[3,10] it must be stressed that in this study we are likely dealing with a heterogenous group of patients.

To date, the use of cimetidine has been reported in numerous trials involving more than 700 patients with gastroesophageal reflux disease (Table 3). The definition of gastroesophageal reflux disease varied from study to study. In addition, the severity of reflux disease varied greatly; in some studies patients had symptomatic reflux without endoscopic signs of esophagitis, whereas in others the patients had severe esophagitis, ulceration or stricture. Patients were treated for periods varying from 4 to 12 weeks with doses of cimetidine varying from 1 to 2 grams per day. In 13 of these 18 (72%) studies, there was significant improvement in the patients' symptoms in the cimetidine-treated groups (Table 3). In 7 of 14 (50%) studies, there was endoscopic improvement and in 3 of 7 studies (43%), the short-term treatment of esophagitis was associated with improvement histologically. There was generally no correlation among the improvement in the patients' symptoms or endoscopic or histologic findings. For example, there was endoscopic and histologic but not symptomatic resolution in the study of Wesdorp and co-workers,[11] whereas symptomatic and histologic but not endoscopic improvement occurred in the study of Fiasse and associates.[12] Of the seven studies showing a significant improvement in the endoscopic appearance of the esophagus in patients treated with cimetidine, five reported symptomatic improvement. We should stress that in all of these studies, patients had free access to antacids, and patients taking cimetidine often consumed less antacid than did patients taking a placebo. None of the studies had pretreatment stratification for smoking or for obesity. Our study adds 118 more patients with esophagitis in whom improvement in the symptoms of gastroesophageal reflux disease was noted with the use of cimetidine (Figures 1 and 2). In more than half of the patients healing was observed endoscopically after eight weeks of therapy (Figure 3). With both therapeutic regimens—cimetidine, 600 mg twice a day and 300 mg four times a day—the diminution in daytime and nighttime pain was gratifying.

Other authors stress the possible role of cimetidine in resolving mucosal sensitivity, as assessed by the acid perfusion test, esophageal manometry or overnight pH monitoring. Two studies reported significant cimetidine-associated improvement by pH monitoring.[22,29] One reported significant improvement[30] and three reported no improvement in the results of the Bernstein test.[10,11,18] None of the three studies using manometry showed improvement as a result of treatment with cimetidine.[11,18,21]

This randomized trial did not include a placebo group. However, numerous previous placebo-controlled studies have shown a superiority of cimetidine therapy over placebo for the symptomatic improvement of gastroesophageal reflux disease, whereas half of the studies showed improved endoscopic findings (Table 1). In view of the proven benefit of cimetidine therapy in patients with gastroesophageal reflux disease (Table 3) and the fact that almost half of the patients entered in this study had benefited from cimetidine use in the past, it was considered unacceptable to withhold this therapy and thereby have a group of placebo-treated "control" subjects. The results obtained in this study, however, are comparable with those observed in the cimetidine-treated patients reported by others. For example, a placebo-controlled study reported by Bennett and colleagues[25] showed a significant reduction in night pain in 51 patients treated with 1 or 2 grams of cimetidine daily for six weeks, as compared with 33 patients treated with placebo plus antacids. Antacid consumption was reduced by about 50% in the cimetidine-treated patients. In a large multicenter placebo-controlled study involving 94 persons with gastroesophageal reflux disease, Behar and colleagues[13] compared the efficacy of cimetidine therapy, 300 mg given four times a day for eight weeks. The

improvement in symptomatology and reduced antacid use was superior to that noted in the placebo-treated patients: the average number of episodes of daytime pain declined in the cimetidine group from about five to two, and the average number of episodes of nighttime pain declined from two to less than one. While this symptomatic improvement in the cimetidine-treated groups noted in these two studies was comparable with the results observed in our study (Figures 1 and 2), cimetidine therapy did not improve the endoscopic appearance of the esophagitis in the study of Behar and coworkers,[13] whereas endoscopic improvement was noted in our study (Figure 3). In our study, both treatment groups showed similar symptomatic improvement between pretreatment and four weeks and between pretreatment and eight weeks (Figures 1 and 2).

From the patients' perspective, the dramatic improvement in symptoms was welcome, and treatment was considered to be overall successful. The incidence of side effects in patients taking the usual total daily dose of 1,200 mg of cimetidine is low.[30] We also noted a low incidence of side effects (Table 2). This was a short-term study, however. It is possible that some patients might have a recurrence of symptoms and possibly a worsening of their esophagitis once treatment with H_2-receptor antagonists has been discontinued. In this study we did not address the important question of the possible need for low-dose maintenance therapy with cimetidine to prevent recurrence of disease.

Sonnenberg and associates[31] examined 30 patients with gastroesophageal reflux and esophagitis treated for 6 to 12 weeks with 1.6 grams per day of cimetidine. The mucosal defects healed in 6 patients, improved in 14 and remained unchanged in 10. Lower esophageal sphincter pressure, acid clearance, results of the acid perfusion test and histologic signs of mucosal infiltration did not improve after healing of the mucosal defects. It is of concern that both in the previous study of Sonnenberg and co-workers[31] and in our study, about a third of the patients with grade 5 endoscopic esophagitis had no improvement during eight weeks of therapy with cimetidine. The persistence of these abnormalities might explain the tendency of esophagitis to recur after symptomatic and endoscopic "healing." It has been suggested that longer periods of therapy might be needed to achieve healing or to prevent the recurrence of esophagitis.[31] However, treating patients with gastroesophageal reflux disease for 12 months with ranitidine therapy failed to achieve further symptomatic, endoscopic or histologic improvement beyond that achieved after eight weeks of treatment.[26]

Accepting the variations in the definition of gastroesophageal reflux disease, the variable endpoints and the likely heterogeneity of the patients, what improvement might we reasonably expect for our patients treated with cimetidine? Significant symptomatic improvement was reported in about two thirds of the studies presented in Table 3. Of the studies using endoscopy, a third reported significant endoscopic improvement with the use of cimetidine. Histologic findings significantly improved in a third of the studies addressing this variable. Patients will likely consume less antacid while taking cimetidine, but there is unlikely to be a consistent change in the results of the Bernstein test, pH monitoring or esophageal manometry.

TABLE 3.—*H_2-Receptor Antagonists in Treatment of Gastroesophageal Reflux Disease*

Study Source	Number of Patients	Symptoms*	Significant Effect*			
			Endoscopy	Histology	Antacid	Tests†
Cimetidine Therapy						
1978 Wesdorp et al[11]	24	−	+	+	−	B−,M−
Behar et al[13]	94	+	−	...	+	B+
Powell-Jackson et al[14]	27	+	−	−	+	B−
1979 Brown[15]	22	+	+	+	+	...
Ferguson et al[16]	20	−	+	−	−	...
Lepsien et al[17]	36	+	−	−	+	...
	22‡	+	+	...	+	...
Petrokubi and Jeffries[18]	15	+	+	...	+	M−
1980 Bright-Asare and El-Bassoussi[10]	50	−	−	...	...	B−,M−
Festen et al[19]	20	−	−	...	−	...
Fiasse et al[12]	34	+	−	+	+	...
Druguet and Lambert[20]	82	+	+	...	−	...
Thanik et al[21]	43	+	+	...	−	...
Bennett et al[22]	68	+	...	...	+	pH+
	18‡	−	...	...	...	pH−
1981 Greaney and Irvin[23]	20	−	−	...	...	...
1982 Bradby et al[24]	43	+	...	−	...	...
1983 Bennett et al[25]	84	+	...	...	+	pH+
Total	722					
Ranitidine Therapy						
1982 Sherbaniuk et al[26]	73	+	+	−	+	
1982 Berstad[27]	168	+	+	−	+	
1983 Wesdorp et al[28]	36	+	+	+	+	
Total	277					

*The symbol + signifies that significant improvement occurred, − indicates that there was no significant improvement.
†B = Bernstein test, M = esophageal manometry and pH = pH monitoring.
‡Two groups of patients were reported.

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